Pulmonary aspergillosis and cryptococcosis coexist in a patient with rheumatoid arthritis and tuberculosis

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Abstract: Combined infection of *Aspergillus* and *Cryptococcus* in the lung is extremely rare. Here, we present a case of concomitant occurrence of pulmonary aspergillosis and cryptococcosis coexisting in a 58-year-old Chinese woman with rheumatoid arthritis and tuberculosis. Pulmonary aspergillosis and cryptococcosis was diagnosed by histopathology of lung tissues by surgery. She was administered oral voriconazole 400 mg/d for 3 months, and was followed up for 2 years with on evidence of recurrence. It is necessary to take aspergillosis and cryptococcosis into consideration in a case of cavitary pulmonary lesions caused by tuberculosis.
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KeyWords: Aspergillosis; Cryptococcosis; Rheumatoid arthritis

1. Introduction

Cryptococcus is an encapsulated fungus, which is wide-spread in rotten food, soil and bird droppings, especially dove droppings. Cryptococcosis is a potentially fatal fungal disease, which is caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. Aspergillosis is caused by genus *Aspergillus*, and most people inhale *Aspergillus* spores every day. [1] Cryptococcosis and Aspergillosis are both opportunistic infection in human and mainly affect immunocompromised patients, such as acquired immune deficiency syndrome (AIDS) and the expanded use of immunosuppressive drugs. Althought *Cryptococcus* and *Aspergillus* are ubiquitous fungus and often infect human lungs, combined infection of *Aspergillus* and *Cryptococcus* in the lung is extremely rare. Here, we present a case of pulmonary aspergillosis and pulmonary cryptococcosis coexisting in a relatively immunocompromised individual with rheumatoid arthritis (RA) and tuberculosis in South China.

2. Case Report

A 58-year-old Chinese woman presented to our hospital complaining of cough and hemoptysis for 3 months. She reported significant weight loss of 10 kg, but no fever, night sweat, irritability, dysphagia, dyspnea, headache, dizziness, nausea or vomiting. Ten years ago, she had been diagnosed with RA and took irregularly oral non-steroidal anti-inflammatory drugs and prednisone. She had a 4-year history of tuberculosis, and took regularly oral isoniazid, rifampicin and ethambutol in the first year after the diagnosis. She didn't have smoking history and didn't report any history of trauma. She denied exposure to any infectious patients and any history of infusion. She was a native resident and worked as a housewife.

Physical examination revealed a body temperature of 36.7°C, blood pressure of 105/78 mmHg, heart rate of 76 beats/min, respiratory rate of 18 breaths/min, body weight of 42 kg, and body mass index of 17.5 kg/m^2. The patient appeared to be in poor nutritional condition. Cardiac, thoracic and abdominal examinations were normal. There were no skin lesions.

The erythrocyte sedimentation rate (ESR) was 33 mm/h (normal: <20 mm/h), the C-reactive protein (CRP) was 30.2 mg/dL (normal: <0.8 mg/dL), and rheumatoid factor (RF) of 90.8 IU/mL (normal: <40IU/mL). Routine blood tests revealed anemia, with a hemoglobin of 9.6 g/dL (normal: 11.0-16.0 g/dL). Tumor markers (including alpha fetoprotein, carcinoembryonic antigen, β2-microglobulin, ferroprotein and estradiol) were within normal range. The serological tests forHIV syphilis, and cryptococcal antigen were negative. Acid-fast bacillus test of sputum smear was negative. The concentrations of plasma electrolytes, total bilirubin, creatinine, urea nitrogen, and albumin were within normal ranges. The abdominal ultrasonography examination was normal. Computed tomography (CT) of the chest demonstrated that high density shadow and cavitation in the posterior segment of right superior lung was probably tuberculous cavity and fungal infection, and high density shadow in the left superior lung was probably tuberculosis (Figure 1). The result of fiber bronchoscopy examination was normal. A definitive diagnosis could not be established at this stage. The patient was underwent wedge resection of right superior lung under vadio-assisted-thoracic-surgery (VATS). During the surgery, we observed that the

posterior segment of right superior lung adhered to chest wall. The taupe specimen was about 10cm×6cm×3cm in size with thickened bronchial wall and broadening lumen, and there were 3 gray nodules in the section. The specimen was sent for histopathological analysis, and for culturing of bacteria, mycobacteria and fungi. Histopathologically, the nodule consisted with granulomatous inflammation. Gomori's methenamine silver (GMS) and periodic acid-Schiff (PAS) staining detected spherical organisms consistent with *Cryptococcus* (Figure 2). Numerous hyaline hyphae that divided into branches at 45° consistent with *Aspergillus* were observed in the broadening bronchial lumen (Figure 3). Culture of the surgical specimen revealed the growth of *Aspergillus*. Antifungal susceptibility showed that the fungus was sensitive to voriconazole and itraconazole. Bacteria and mycobacteria culture, however, were negative.

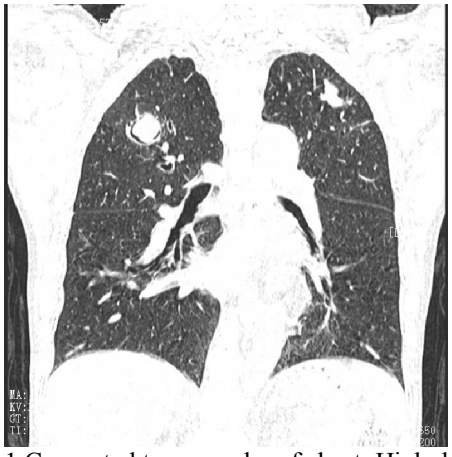

Figure 1 Computed tomography of chest. High density shadow and cavitation in the posterior segment of right superior lung was probably tuberculous cavity and fungal infection, high density shadow in the left superior lung was probably tuberculosis.

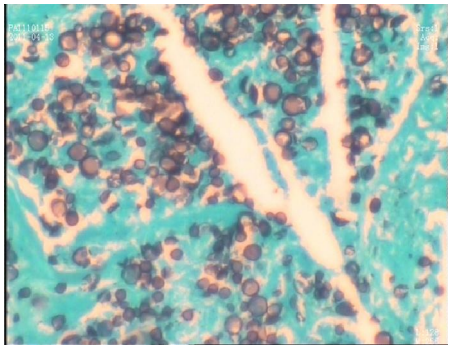

Figure 2 Pathology of tissues from the lung cavity showed spherical organisms consistent with Cryptococcus. (Gomori's methenamine silver, ×400)

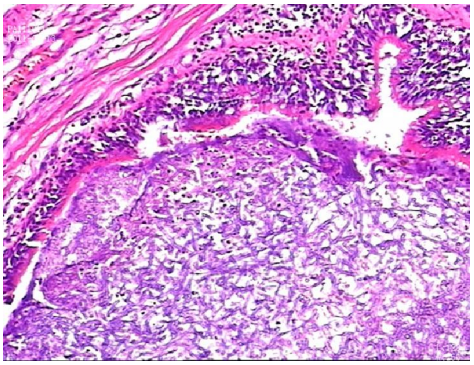

Figure 3 Numerous hyaline hyphae that divided into branches at 45° consistent with *Aspergillus* were observed in the broadening bronchial lumen. (Hematoxylin & Eosin, ×400)

The patient was diagnosed with concomitant occurrence of pulmonary aspergillosis and cryptococcosis. She was administered with voriconazole 400 mg/d orally for 3 months. There were no significant adverse effects or discomfort during the treatment. The patient was discharged after her wound healed well. She was followed up for 2 years without evidence of recurrence.

3. Discussion

Cryptococcosis and aspergillosis are both believed to be acquired by inhalation of the conidia from the environment. They are mainly affects the immunocompromised patients, such as AIDS and individuals using immunosuppressive drugs. In our case, she had a 4-year history of tuberculosis and a 10-year history of RA, and took irregularly oral prednisone. Long-term irregularly corticosteroid therapy may damage the immunity.

Human lungs are the most frequent organs infected by *Aspergillus* and *Cryptococcus*. However, coinfection with pulmonary aspergillosis and cryptococcosis in a patient is extremely rare, [2-5] and mainly developed in immunocompromised patients with AIDS, systemic lupus erythematosus (SLE), and steroid-induced diabetes mellitus. Only one case of pulmonary cryptococcosis in an old tuberculous cavity coexistence with pulmonary aspergillosis was reported. [6] Therefore, to the best of our knowledge, this is the first report of pulmonary aspergillosis and cryptococcosis coexisting in a Chinese woman with rheumatoid arthritis and tuberculosis.

Definite diagnosis of pulmonary aspergillosis and cryptococcosis in immunocompromised patients may be difficult. They may be asymptomatic or presented with nonpathognomonic symptoms, including cough, hemoptysis, fever, chest pain and dyspnea. The diagnoses can be confirmed by histopathology and fungal culture from specimens of

sputum and lung tissue. Many laboratory experiments and auxiliary examination, including polymerase chain reaction, serological tests, CT and positron emission tomography scans, bronchoscopy, mediastinoscopy, and VATS can help to establish the diagnoses. [7] Lung biopsy is widely recognized as a valuable method for the diagnosis and management of diverse pulmonary disorders. Lung tissue with definite diagnosis can be obtained by CT-guided needle biopsy, open thoracotomy, or by VATS. Surgical lung biopsy is safe and effective for diagnosis. Surgical lung biopsy for immunocompromised patients with unexplained pulmonary processes can be performed within acceptable levels of risk and significant benefits. [8] In our case, pulmonary aspergillosis was diagnosed by fungal culture and lung biopsy, and pulmonary cryptococcosis was diagnosed by lung biopsy. Voriconazole is recommended as the first line antifungal in *Aspergillus* infection. [9] Although amphotericin B combined with flucytosine is the first line therapy for cryptococcosis in immunocompromised patients, voriconazole is also effective for the fungal infection and recommended as salvage therapy for the disease. [10-11] Consequently, we treated the patient with voriconazole, and the prognosis was very satisfactory, as the follow-up results indicated.

In summary, we report a unique case of concomitant occurrence of pulmonary aspergillosis and pulmonary cryptococcosis in a Chinese woman with RA and tuberculosis. It is necessary to take aspergillosis and cryptococcosis into consideration in a case of cavitary pulmonary lesions caused by tuberculosis. We found that surgical removal of the lesion and systemic treatment with antifungal were effective for control of the infections.

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